Neurologic complications following treatment of canine hypoadrenocorticism

Karen L. MacMillan

Abstract — After treatment for hypoadrenocorticism, an 18-month-old dog exhibited marked ataxia and intermittent muscle tremors, progressing to head pressing, dysphagia, and quadraparesis. Serum sodium increased by 38.9 mmol in 48 hours, suggesting myelinolysis. The dog made a complete recovery after intensive treatment.

Résumé — Complications neurologiques d'un traitement contre l'hypoadrénocorticisme. À la suite d'un traitement contre l'hypoadrénocorticisme, un chien de 18 mois a présenté une ataxie marquée ainsi que des tremblements musculaires intermittents qui ont progressé jusqu'à un état de «pousse au mur», de dysphagie et de quadraparésie. Le sodium sérique a augmenté de 38,9 mmol en 48 heures, ce qui laisse supposer une myélinolyse. Le chien s'est complètement rétabli après des soins intensifs.

(Traduit par Dre Andrée Lesage)

Can Vet J 2003;44:490–492

An 18-month-old, intact, male West Highland white terrier was presented with a history of lethargy, vomiting, anorexia, and apparent discomfort. Prior medical history was unremarkable. However, the dog had been vaccinated with a modified-live multivalent vaccine (DA2PPv; Scherling, Omaha, Nebraska, USA) and a killed rabies vaccine (Merial, Athens, Georgia, USA), 1 mo earlier.

On initial examination, pain was not evident. The dog was depressed and 10% dehydrated, with no sign of diarrhea. A blood sample was collected for a complete blood cell (CBC) count (QBC Autoreader; IDEXX Laboratories, Westbrook, Maine, USA) and serum biochemical analysis (Vet Test 8008; IDEXX Laboratories). Results were unremarkable, except for mild lymphocytosis (8.3×10^9/L; reference range, 1.1 to 6.3×10^9/L); mild azotemia (urea nitrogen 16.3 mmol/L; reference range, 2.5 to 9.6 mmol/L), and a slightly elevated alanine aminotransferase (ALT) (112 U/L; reference range, 10 to 100 U/L). Lateral thoracic and ventrodorsal abdominal radiographs were unremarkable. Differential diagnoses included gastroenteritis, nephropathy, and hypoadrenocorticism. Lactated Ringer's solution (LRS; Abbott Laboratories, Saint-Laurent, Quebec) was administered at a rate of 2.6 mL/kg bodyweight (BW)/h over 24 h. As the dog's appetite and attitude had improved, it was released on the following day on treatment: enrofloxacin (Baytril; Bayer, Toronto, Ontario), 4 mg/kg BW, PO, q12h for 10 d.

Six hours after release, the owner reported that the dog was not moving and had very red gums. On presentation, the dog's capillary refill time and mucous membrane color were normal, and there was no sign of dehydration or report of vomition or anorexia. The dog stood with an arched back and walked with a tucked up abdomen. A painful mass was evident caudal to the prostate on deep digital palpation. On the basis of the history and physical examination, differential diagnoses included prostatic abscess or cyst, prostatic neoplasia, lymphadenitis, and prostatitis.

On day 4, the dog was anorexic. Other abnormal findings included severe lethargy, marked generalized weakness, 5% dehydration, hypothermia (35.5°C; reference range, 37.5°C to 39.5°C), and hematochezia. On day 5, the CBC count was within normal limits, but serum biochemical results showed a hypocholesterolemia (2.2 mmol/L; reference range, 2.8 to 8.3 mmol/L), a hyperkalemia (7.65 mmol/L; reference range, 3.50 to 5.80 mmol/L), and a hypochloremia (79.8 mmol/L; reference range, 109.0 to 122.0 mmol/L). An adrenocorticotropic hormone (ACTH) stimulation test (Cortrosyn; Organon, Scarborough, Ontario; 0.25 mg/kg BW, IV) was performed on day 6 to detect hypoadrenocorticism. Pending results of this test, the dog was treated with prednisolone sodium succinate (Solu-Delta-Cortef; Upjohn, Mississauga, Ontario), 17 mg/kg BW, and dexamethasone (Azium; Schering, Pointe-Claire, Québec), 2.5 mL, IV, administered slowly. Instead of lactated Ringer's solution, warm 0.9% NaCl (Baxter Corporation, Toronto, Ontario) was administered, 5 mL/kg BW/h, IV, over 24 h. Oat bags and blankets were used to warm the dog to normal body temperature range.

Hypoadrenocorticism was confirmed by the results of the ACTH stimulation test. Serum cortisol was

Ontario Veterinary College, University of Guelph, Guelph, Ontario N1G 2W1.

Dr. MacMillan's current address is Bay Cat and Dog Hospital, 525 King Street East, Toronto, Ontario M5A 1M3.

Address all correspondence and reprint requests to Dr. MacMillan.

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< 0.36 nmol/L, both before (reference range, 15 to 120 nmol/L) and 1 h after (reference range, 220 to 550 nmol/L) injection with ACTH. Hydrocortisone sodium succinate (Solu-cortef; Upjohn, Mississauga, Ontario) was administered, 5 mg/kg BW, IV. In addition, the dog was treated with sucrulfate (Carafate; Hoechst Marion Roussel, Laval, Québec), 0.1 mg/kg BW, PO, q8h, and the IV saline drip was continued. Within 24 h, serum sodium increased from 97.7 to 119.5 mmol/L, and serum chloride increased from 79.8 to 99.9 mmol/L. That evening (day 6), the dog became less responsive and exhibited marked weakness and ataxia when walked outside.

By day 7, the sodium levels had further increased to 136.6 mmol/L. Fludrocortisone acetate (Florinef; Apothecon, Mississauga, Ontario), 0.02 mg/kg BW, PO, q24h, and prednisone (Apo-prednisone; Apotex, Toronto, Ontario), 0.2 mg/kg BW, PO, q24h, were prescribed and the IV saline drip was continued. Although the dog was responsive only to the owner, he readily ate and drank.

On day 8, serum sodium had increased to 137.6 mmol/L, with continued hypochloremia (106.6 mmol/L). Neurologic signs had progressed to intermittent muscle tremors involving the head, moderate depression, marked generalized weakness with incontinence, anorexia, and polydypsia. A CBC count on day 9 showed anemia (hematocrit 0.23 L/L; reference range, 0.37 to 0.55 L/L; hemoglobin 84 g/L; reference range, 120 to 180 g/L) with minimal signs of regeneration. A serum biochemical profile revealed hypoalbuminemia (20 g/L; reference range, 27 to 38 g/L), decreased amylase (254 U/L; reference range, 500 to 1000 U/L), hypocholesterolemia (1.9 mmol/L; reference range, 2.8 to 8.3 mmol/L), hypoproteinemia (43.8 g/L; reference range, 52 to 82 g/L), and hypoglobinemia (22.8 g/L; reference range 25 to 45 g/L). Serum electrolyte parameters were normal.

During days 9 to 11, the dog appeared severely depressed and, unless stimulated, remained in lateral recumbency, apparently unaware of its surroundings. There was partial anorexia with an increasing need to be hand-fed; however, the dog drank when water was offered. The progressive neurologic signs, including progressive pelvic limb ataxia with a tendency to fall to the left side, quadriparesis, and intermittent dysphagia, were indicative of brainstem dysfunction with possible thalamocortical and spinal cord involvement. The diagnosis included encephalopathy secondary to hyponatremia. When such neurological signs are exhibited, a renal or hepatic disease, encephalitis, or lead ingestion must also be considered (1).

Between days 12 and 19, the neurologic condition improved progressively. The dog remained moderately depressed, with periods of hind limb muscle tremors and head pressing in the kennel, but also became more active and displayed intermittent episodes of excitement. The dog was able to support weight and take small steps without falling; it started to respond to hospital staff and to consume food with little difficulty.

On day 30, the dog was released from the hospital with instructions that stressful situations might require increased drug dosages, as directed by a veterinarian. The client was educated on glucocorticoid and mineralocorticoid supplementation with fludrocortisone acetate, 0.02 mg/kg BW, PO, q24h, and prednisone, 0.2 mg/kg BW, PO, q24h.

The history and physical examination findings in this case were typical of hypoadrenocorticism and prostatitis. West Highland white terriers are predisposed to hypoadrenocorticism, with onset reported as early as 10 mo of age. Hypoalbuminemia, hypocholesterolemia, and anemia have all been reported with uncomplicated hypoadrenocorticism (1). This case was unusual in the development of a biphasic progressive central nervous system disease that changed during treatment of hyponatremia, secondary to hypoadenocorticism. Hyponatremia causes generalized encephalopathy, characterized by malaise, nausea, lethargy, confusion, seizures, coma, and death (2). In this dog, the progression of neurological signs after correction of hyponatremia suggested a diagnosis of generalized encephalopathy, specifically, myelinolysis.

Myelinolysis is a symmetrical, noninflammatory, demyelination of central pontine regions associated with the rapid correction of chronic hyponatremia with IV fluids (3). Neuronal cell bodies and axons are generally spared (3). Serum sodium concentration reflects the amount of sodium relative to water in the extracellular fluid (ECF). With the loss of serum sodium, shifting of water from the ECF space to the intracellular fluid (ICF) space causes cellular swelling and cerebral edema (4). Cerebral edema causes increased intracranial pressure, precipitating neurologic symptoms (1), with the severity of neurologic symptoms being dependent on the rate of development and degree of the hyponatremia (4). A sudden, rapid fall in serum sodium may induce seizures and coma, whereas chronic hyponatremia, such as that associated with hypoadrenocorticism, produces moderate encephalopathy (2).

During chronic hyponatremia, adaptive solute translocation occurs in the brain, preventing severe damage due to cerebral edema (1,3). Cells in the brain synthesize pumps to extrude cations and organic solutes (1). Sodium; potassium; chloride; and other solutes, such as glutamine, glutamate, taurine, myoinositol, and phosphocreatine, rapidly exit the cell (1,3). As a result of these translocations, equilibration of the osmotic gradient between the ECF and the ICF occurs within 2 to 3 d (1). However, the brain requires up to 1 wk to reverse these adaptive changes after the serum sodium concentrations increase (1). With rapid treatment of chronic hyponatremia, the cells are at risk of osmotic stress as the plasma becomes hypertonic relative to the ECF (1,3). Administration of sodium in IV fluids causes plasma to become hypertonic, which causes cerebral dehydration, intramyelin edema, breakdown of the blood brain barrier, and oligodendrocyte degeneration (1). Full recovery of neurologic function after myelinolysis is possible. In this case, the dog displayed neurologic complications for 3 d before improvements were observed. Total recovery from myelinolysis occurred within 2.5 wk from the onset of neurologic sequelae.

Guidelines to prevent myelinolysis during correction of hyponatremia vary in the literature. Soupart et al (5) state that the risk of brain myelinolysis can be largely reduced by limiting the rate of serum sodium correction

to 15 mmol/L over 24 h. However, when other risk factors for myelinolysis are present (hypokalemia, liver disease, poor nutritional state, and burns), correction should not exceed 10 mmol/L over 24 h (3,5). Laureno et al (2) reported that in 21% of 14 human cases, myelinolysis developed after a correction of 15 mmol/L over 24 h. In an earlier study, 71% of the dogs showed myelinolytic lesions when serum sodium levels increased more than 14 mmol/L during the first 24 h (2). These data suggest that correction of chronic hyponatremia should be limited to $<$ 10 mmol/L over 24 h. In this case, fluid therapy with 0.9% NaCl resulted in an increase in serum sodium concentration of 21.8 mmol/L in the first 24 h, with a further increase of 17.1 mmol/L in the next 24 h, which clearly exceeds current guidelines. Electrolyte levels may increase unexpectedly and should be closely monitored during treatment of hyponatremia.

The amount of sodium required to restore normal sodium levels is calculated by the following equation: Na^+ deficit (mmol/L) = (0.6 $\times$ BW in kg) $\times$ (140 $-$ Na^+ mmol/L) (4). A solution of 0.9% NaCl contains 150 mmol/L of Na^+. The total volume of fluid that can be safely used in a 24-hour period can be calculated by the following equation: Volume 0.9% NaCl (L) = (10 mmol/L/24 h $\times$ TVF) $\div$ (140 $-$ Na^+), where TVF represents the total volume of fluid (L) to correct the Na^+ deficit, and Na^+ is the patient's serum Na^+ in mmol/L (1).

Treatment of hypoadrenocorticism should focus on relieving hypotension, hypovolemia, and electrolyte imbalances, such as hyperkalemia, hyponatremia, and hypochloremia, while providing adequate glucocorticoid and mineralocorticoid supplementation.

Acknowledgments

The author thanks the staff of the Allandale Veterinary Hospital, Barrie, Ontario for their guidance on this case and Sandra Lunik for help with the manuscript. CVJ

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